Regulatory Science for R&D Promotion of Innovative Pharmaceuticals*

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BACKGROUND

At present the nation’s policy for research and development (R&D) promotion of innovative pharmaceuticals and improvement of environments for the R&D is formulated by Japanese government. In the policy, the enhancement and promotion of Regulatory Science (RS) touching the appropriate and rapid predict, evaluate, and judgment of quality, efficacy and safety of pharmaceuticals is especially stressed. Following the nation’s policy, the Ministry of Health, Labor and Welfare (MHLW), the Pharmaceuticals and Medical Devices Agency (PMDA), the National Institute of Health Sciences (NIHS), and Japan Agency for Medical Research and Development (AMED) are carrying out the activities to promote the R&D, cooperating with each other, academia, industry, or the other government bodies.
New expedited approval system under PMD Act - Conditional/term-limited authorization -

< Drawback of traditional PAL approval system >
Long-term data collection and evaluation in clinical trials, due to the characteristics of cellular/tissue-based products, such as non-uniform quality reflecting individual heterogeneity of autologous donor patients

[Traditional approval process]

Clinical study

- Phased clinical trials (confirmation of efficacy and safety)

- Marketing authorization

- Marketing

[New scheme for regenerative medical products]

Clinical study

- Clinical trials (likely to predict efficacy, confirming safety)

Conditional/term-limited authorization

Marketing (Further confirmation of efficacy and safety)

Re-application within a period (max. 7 yrs)

Marketing authorization or Revocation

Marketing continues

Post-marketing safety measures must be taken, including prior informed consent of risk to patients
Two of the new product approvals under the new regulation (Update)

• In September and in October 2014, two new product applications for marketing authorization were filed by PMDA.

• They were approved on 18 September 2015.

1. Bone marrow mesenchymal stem cells (MSCs) for GVHD (normal approval)
2. Skeletal myoblast sheet for serious heart failure due to ischemic heart disease (conditional and time-limited authorization – 5 years, conducting post-marketing efficacy studies)

Note: Figures quoted from the company press release docs
**SAKIGAKE Designation System**

**SAKIGAKE** is a system to put into practice innovative medicines/medical devices/regenerative medicines initially developed by Japan.

### Designation Criteria

Medical products for diseases in urgent need of innovative therapy which may satisfy the following two conditions:

1. **Having firstly developed in Japan and planned an application for approvals (desired to have PMDA consultation from the beginning of R&D)**
2. **Prominent effectiveness (i.e. radical improvement compared to existing therapy), can be expected based on the data of mechanism of action, non-clinical study and early phase of clinical trials (phase I to II)**

### Designation Advantage

1. **Prioritized Consultation**
   - Waiting time: 2 months → 1 month
   - Shortening a waiting time for a clinical trial consultation from the submission of materials.
2. **Substantial Pre-application Consultation**
   - [de facto review before application]
   - Encouraging Consultation
   - Accepting materials in English
3. **Prioritized Review**
   - 12 months → 6 months
   - Targeting total reviewing time: 6 months
   - Accept the result of phase III study after the application on a case-by-case basis to shorten the time from R&D to approval
4. **Review Partner**
   - [PMDA manager as a concierge]
   - Assign a manager as a concierge to take on overall management for the whole process toward approval including conformity assurance, quality management, safety measures, and reviewing application
5. **Substantial Post-Marketing Safety Measures**
   - Extension of re-examination period
   - Strengthening post-marketing safety measures such as extension of re-examination period after approvals well as facilitating coalition with scientific societies, and global information dissemination.

### Designation Procedure

1. **Option 1:** Application is to be submitted to Evaluation and Licensing Division (ELD) and to be reviewed by PMDA. The result of designation is to be notified within 60 days.
2. **Option 2:** ELD is to approach a potential applicant. The result of designation is to be notified within 30 days after the submission, if agreed by the applicant.
General Timeframe of SAKIGAKE

【Ordinal Review】
1. Consultation
2. Clinical Trial Phase I/II
3. Consultation on Clinical Trial
4. Clinical Trial Phase III
5. Review
6. Covered by Insurance
7. Commercialization in market

【Review under SAKIGAKE Designation System】
1. Priority Consultation
2. Prior Review
3. Priority Review
4. Review Partner
5. Practical application of innovative medical products
6. Strengthening post-marketing safety measures (re-evaluation period)
Accumulation and utilization of electronic-data

NDA submission
- e-Submission of data
  - Submission of electronic data from clinical and nonclinical studies
- Storage of electronic data in the dedicated server and registration in the database

Regulatory Review
- Use of electronic data
  - Accessible, visualized electronic data for each reviewer
  - Easy to identify individual clinical case data, drilling down of data
  - Operation of various analyses - simple, subgroup analysis for the present
- Visualization and analysis of data, supported by browsing software

Utilization of Accumulated Data
- Integration of cross-products information
  - Utilization of exhaustive information by therapeutic category for review/consultation
  - Internal review on particular theme – e.g.) active utilization of M&S
    - Review on pediatric dosage
    - Preparation of disease model
    - Development of evaluation indicator
  - Utilization in preparation of guideline

What the review authority can do with the information of all products.

Submission of electronic clinical study data has started since Oct 1st 2016!

Scientific discussion and decision making on the basis of internal analysis result

Contribution to efficient development through review/consultation and GL publication based on further analyses by dry-lab.
Prospect of e-Study data utilization in Japan

Prospect As of Feb 2017 (Subject to Change)

- J-FY2017
  Setup e-data management and utilization

- J-FY2018
  Ordinary utilization of e-data in the product review

J-FY2019 - 2021
Starting earnest cross-product analysis

Transitional period are taken until March 31st, 2020
- Preparations of guidelines and related documents
- Earnest on cross-product analysis and development of disease models

J-FY2022 -
Publication of guidelines to contribute to drug development
- Establishment of disease models
- Publication of disease-specific guidelines

First-class review authority

Set start e-study data submission for NDA* from Oct 1st, 2016
*NDA=New Drug Application
- More predictable efficacy/safety
- Consideration of expanding the scope of e-data utilization to toxicological study and post-approval clinical study
- Industries’ workload is reduced gradually while keeping the review period

Prospect As of Feb 2017 - March 2018

• Preparations of guidelines and related documents
• Earnest on cross-product analysis and development of disease models

Prospect As of Feb 2017 - March 2018

Publication of guidelines to contribute to drug development
- Establishment of disease models
- Publication of disease-specific guidelines

- J-FY2022
  - Establishment of disease models
  - Publication of guidelines to contribute to drug development

Prospect As of March 2018

e.g. guidelines and disease models based on data on Asian population

Setup e-data management and utilization

Promotion of paperless operation

Start e-study data submission for NDA* from Oct 1st, 2016
*NDA=New Drug Application
• More predictable efficacy/safety
• Consideration of expanding the scope of e-data utilization to toxicological study and post-approval clinical study
• Industries’ workload is reduced gradually while keeping the review period
• The Medical Information Database Network in Japan for a real-time assessment of drug safety (currently 4M patients)
• MID-NET will start full-scale service from 2018FY
In near future

- Quantitative risk assessment compared with control

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Number of patient with Hypocalcemia</th>
<th>Incidence proportion</th>
<th>Relative risk</th>
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<tbody>
<tr>
<td>Denosumab</td>
<td>190</td>
<td>93</td>
<td>0.489</td>
<td>1.35</td>
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<tr>
<td>Zoledronic acid</td>
<td>245</td>
<td>89</td>
<td>0.363</td>
<td></td>
</tr>
</tbody>
</table>

Data from 3 hospitals (2013/7～12)

Launched (2012.4.17)

Spontaneous ADR reports (～2012.8.31)
- serious Hypocalcemia: 32 cases
- death: 2 cases

Dear healthcare professionals letter (2012.9.12)

MID-NET will contribute to regulatory action (Trial analysis: Denosumab for Hypocalcemia)
The Science Board was established in May 2012 to discuss how PMDA can better cope with products with advanced science & technology, in each developmental stage (basic research, development support, product review, and PMS).

**Topics in the 3<sup>rd</sup> term**

1. Clinical evaluation of rare cancer
2. Facilitating R&D of Academia-originated Pharmaceuticals
3. Artificial Intelligence and its application in medical field

**Board members**
Academia (Knowledge of the Latest Innovative Technologies)
AIM: Development and standardization of evaluation methods of cutting-edge pharmaceuticals, medical devices and cellular & tissue-based therapy products

1) Clarification of conditions (confirmation of quality and non-clinical safety) required for the first-in-human study, and development of the evaluation methods

2) Development and standardization of evaluation methods to confirm the usefulness in medical care

3) Clarification of conditions required for approval application, and drafting of guidelines and standards

4) Carrying out official tests, when the problem might happen

5) Global efforts cooperating with foreign regulatory science research organizations
Examples of Regulatory Science for R&D promotion of Cutting-Edge Medical Products

- **Division of Drugs**: Development and standardization of evaluation methods of cutting-edge pharmaceuticals such as nanomedicines and DDS
- **Division of Biological Chemistry & Biologicals**: Development and standardization of evaluation methods of antibody drugs and advanced modified protein drugs
- **Divisions of Biological Chemistry & Biologicals and Organic Chemistry**: Development and standardization of evaluation methods of specialty peptides
- **Divisions of Medicinal Safety Science, Molecular Target & Gene Therapy Products, and Biochemistry**: Biomarkers for personalized medicine, molecular diagnostics, and radioactive diagnostic agents
- **Division of Molecular Target & Gene Therapy**: Development and standardization of evaluation methods of oligo-nucleotide drugs
- **Division of Molecular Target & Gene Therapy**: Development and standardization of evaluation methods of gene therapy drugs
- **Division of Cell-based Therapeutic Products**: Development and standardization of evaluation methods of tissues and cells for cell-based therapy including iPS cells
- **Divisions of Cell-based Therapeutic Products, and Biological Chemistry & Biologicals**: Development and standardization of detection, inactivation and removal methods of infectious agents contaminated in raw materials or products
- **Division of Medical Devices**: Development and standardization of evaluation methods of new biomedical materials including biocompatibility
- **Division of Pharmacology**: Development and standardization of safety pharmacology tests using iPS cells
The promotion of regulatory science for nanomedicines in Japan

- Research for evaluation of nanomedicines
  - Development of suitable evaluation methods and standardization

- Drafting technical guidelines
  - After public consultation, guidelines were issued from the MHLW (Ministry of Health, Labour and Welfare)
    1. Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products
       (January 10, 2014, PFSB/ELS Notification No.011-1)
    2. MHLW Guideline for the Development of Liposome Drug Products
       (March 28, 2016, PSEHB/ELD Notification No. 0328-19) New!
    3. MHLW Reflection paper on nucleic acids (siRNA)-loaded nanotechnology-based drug products
       (March 28, 2016, PSEHB/ELD Administrative Notice) New!

- Exchange of information with international organizations
  (e.g. International Pharmaceutical Regulators Forum: IPRF)
Studies for detection and removal of tumorigenic cells contained in iPS cell-based regenerative medical products

Residual tumorigenic cells/undifferentiated cells in regenerative medical products derived from iPS cells is one of the major concerns in the manufacturing. In this research collaboration among three institutes, we develop in vivo tumorigenicity tests using NOG mice and cytotoxic viral vectors to remove undifferentiated cells in products.

Kawasaki City Institute for Public Health
Development of cytotoxic viral vectors specific for undifferentiated iPS cells

Central Institute for Experimental Animals
Rearing NOG mice, transplantation of cells, and monitoring tumor formation

National Institute of Health Sciences
Preparation of iPS cells and characterization of tumorigenicity tests

Quality assessment (identity and impurity)

Non-clinical safety evaluation

Transplantation

Removal

Differentiated cells after removal of residual undifferentiated cells

Differentiated cells containing residual undifferentiated cells

Differentiation

iPS cells

NIHS

2017/3/26
New System for Medical R&D

Headquarters for Healthcare Policy (HHP)
- develop a comprehensive plan for the promotion of medical R&D
- integrate medical R&D budget requests of relevant ministries
- make strategic decisions on the allocation of promotional adjustment funds

Ministries
- Cabinet Secretariat, Office of Healthcare Policy
- Ministry of Education, Culture, Sports, Science and Technology
- Ministry of Health, Labour and Welfare
- Ministry of Economy, Trade and Industry

Funding
- Japan Agency for Medical Research and Development
  - Provides a unified point of contact for funding and for application procedures.
  - Provides support from basic research to practical use.
Examples of the projects awarded in Research on Regulatory Science of Pharmaceuticals and Medical Devices by AMED in F.Y. 2016

**Seeds exploration**

- Studies on safety evaluation and quality control of biopharmaceuticals and oligonucleotide therapeutics
- Development and international standardization of drug safety assessment using human iPS cell technology
- Study on the safety assessment of genome editing technologies for human gene therapy
- Studies on the bridging procedure of clinical data obtained by the companion diagnostics
- Establishment of frameworks to accelerate international standardization of standards for medical devices

**Quality test**

- Regulatory science research on therapeutic area standards for the development of drugs in Japan
- Establishment of a clinical guideline of endpoints in clinical trials of patients with chronic kidney disease
- Utilization of real world evidence using patient registry data to support regulatory decision-making
- Research on the efficient clinical trial operations according to GCP
- Study on viral shedding and environment risk assessment of genetically modified viruses used in gene therapy clinical studies

**Non-clinical study**

- Research on clinical trial guidance for Medical Device
- Research on data characterization and outcome validation for promoting pharmaco-epidemiological study utilizing MID-NET for benefit-risk assessments
- Analysis of adverse event following immunization and vaccine safety
- The study on transfusion guidelines for patients with massive bleeding
- Identification of genomic biomarkers and involvement of infection on the onset of severe drug adverse reactions.

**Clinical trial**

- Research on the regulation of Stand-alone Software as a Medical Device
- Study on how to set an appropriate post-marketing surveillance period for evaluating use outcomes of implantable medical device
- Establishment of a clinical guideline of endpoints in clinical trials of patients with chronic kidney disease
- Utilization of real world evidence using patient registry data to support regulatory decision-making
- Development and international standardization of drug safety assessment using human iPS cell technology

**Approval review**

- Research on clinical trial guidance for Medical Device
- Regulatory science research on therapeutic area standards for the development of drugs in Japan
- Establishment of a clinical guideline of endpoints in clinical trials of patients with chronic kidney disease
- Utilization of real world evidence using patient registry data to support regulatory decision-making
- Development and international standardization of drug safety assessment using human iPS cell technology

**Post-marketing Safety precaution**

- Research on the regulation of Stand-alone Software as a Medical Device
- Study on how to set an appropriate post-marketing surveillance period for evaluating use outcomes of implantable medical device
SUMMARY of the ACTIVITIES

1. MHLW promotes the strategy package (Strategy of SAKIGAKE) facilitating all the process from R&D, clinical research/trials, pre- and post- marketing safety, insurance coverage, through globalization of innovative products which are to be put into practical use, targeting innovative pharmaceuticals which can cure serious illnesses;

2. PMDA is building up the systems, such as priority consultations, prior assessment, and priority reviews in concert with MHLW, takes various approaches such as the introduction of data mining methods and safety evaluation of drugs based on pharmaco-epidemiological methods utilizing electronic medical records, or construction of medical information database network (MID-NET) to enhance and advance safety measures, and has also established the Science Board consisting of external experts to discuss the evaluation methods of innovative drugs;

3. NIHS has carried out RS research to develop the point-to-consider documents or standardized methods for evaluating mainly quality and non-clinical safety of innovative products such as nanomedicines, fully engineered protein drugs, oligonucleotide drugs, or other medical products; and

4. AMED is supporting about 80 RS research projects by the Grant Program naming “Research on RS of Pharmaceuticals and Medical Devices”.